J Anal Res Clin Med, 2018, 6(1), 28-33.
doi: 10.15171/jarcm.2018.005, *http://journals.tbzmed.ac.ir/JARCM*

Original Article

Investigation of the role of procalcitonin in early diagnosis of infective endocarditis

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Article info
Article History:
Received: 01 Feb. 2018
Accepted: 03 Feb. 2018
ePublished: 10 Mar. 2018

Keywords:
Early Diagnosis,
Infective Endocarditis,
Procalcitonin

Abstract
Introduction: Infective endocarditis (IE) is a life-threatening condition with incidence of 30-100 per million individuals. It is introduced as the 4th disease among life-threatening diseases. The present study was carried out with the aim to compare serum level of procalcitonin (PCT) at the time of diagnosis and at the end of treatment period among patients with IE.
Methods: In this descriptive cross-sectional study which was performed in department of infectious diseases and cardiology on the patients with IE, PCT level was measured at the time of diagnosis and at the end of treatment period.
Results: In this study, 50 patients with IE were evaluated. All of them were febrile. Positive blood culture (PBC) was found among 36% of patients. Involvement of tricuspid valve was detected among 34% of patients. Mean level of PCT was 3.50 ± 13.78 and 14.12 ± 0.00 mg/dl at the time of diagnosis and at the end of treatment period, respectively. Hence, the PCT level at the end of treatment period was significantly lower than that at the time of diagnosis.
Conclusion: PCT along with other laboratory and clinical biomarkers can be useful in primary diagnosis and evaluation of response to treatment among patients with IE.

Citation: Bayat-Makoo Z, Salehi R, Motallemi A, Kavandi H, Naghavi-Behzad M, Moghani AA. **Investigation of the role of procalcitonin in early diagnosis of infective endocarditis.** J Anal Res Clin Med 2018; 6(1): 28-33. Doi: 10.15171/jarcm.2018.005

Introduction

Infective endocarditis (IE) is a life-threatening condition with high rate of morbidity and mortality despite advances in diagnostic and therapeutic methods. Its mortality rate was reported as 40%.[1,2]

Early diagnosis and suitable antibiotic therapy and surgery when necessary lead to a good outcome in the course of the disease.[3]

Diagnosis of infectious endocarditis was proved through using modified Duke Criteria along with clinical findings, microbiological results and imaging.[3] A biomarker with high sensitivity and specificity can increase rate of diagnosis and affect the disease outcome.[1,4,5] Many factors were used for this purpose like rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), circulatory immune complex (CIC), leukocyte count and percentage of premature leukocytes,[3] in addition to procalcitonin PCT which was used in recent studies.[1,6] In addition to contribution to the diagnosis of IE, these biomarkers are useful in evaluating response to antibiotic therapy.[2,3,7] The rate of PCT is

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undetectable (less than 0.01 ng/ml) among the healthy individuals.[8] At the time of stimulation with endotoxin, PCT is produced rapidly by parenchymal tissue of the body.[9] Unlike CRP, PCT does not respond to sterile inflammation and viral infection.[1, 6] This unique feature of PCT makes it valuable in detection of IE.[1]

According to the recent studies, PCT can be used as a marker in early diagnosis of IE. Therefore, the present study was conducted aiming to determine PCT level among patients with IE at the time of diagnosis and at the end of the therapeutic period.

Methods

The present descriptive-analytical study was conducted in Department of Infectious Diseases and Cardiology of Tabriz University of Medical Sciences (Tabriz, Iran). In this study, PCT level was measured at the time of diagnosis and at the end of therapeutic period. In this study, 50 patients with definitive diagnosis of IE based on modified Duke Criteria[10] were evaluated in a period of 2 years in 3 referral hospitals affiliated to the Tabriz University of Medical Sciences.

Serum level of CRP, RF and PCT were measured at the time of admission (before antibiotic therapy) and after completion of antibiotic treatment on the basis of specific microorganisms. ESR and complete blood count (CBC) were measured routinely at the time of admission and discharge after completion of antibiotic treatment. In this study, kits made by DiaSorin Company, Italy were used for quantitative determination of PCT. For this purpose, Sandwich Chemiluminescent Immunoassay (CLIA) method was applied.[2] Using this method, PCT was measured in the range of 0.10-500 ng/ml with cutoff point above 0.25 ng/ml.

The patients with definite diagnose of IE based on Duke Criteria and the patients with complete laboratory data were evaluated in this study. The patients with inadequate and incomplete data and the patients who do not completely fill Duke Criteria and false positive causes of increased PCT (malaria, pancreatitis, burning, traumatic and inhalation injuries, and previous antibiotic use), were excluded from the study.

An informed written consent was received from all participants. In addition, the study protocol was in compliance with the Declaration of Helsinki (DoH) and was approved by the ethics committee of Tabriz University of Medical Sciences. In all stages of the study, patients' information were anonymous and based on codes. In addition, the patients unwilling to take part in the study could leave at any stage.

Results

In this study, 50 patients with IE (27 men and 23 women) were selected and evaluated and the serum level of PCT among them was measured at the time of admission and at the end of the treatment period.

The mean age of patients was 48.77 ± 14.97 and 51.95 ± 14.58 for men and women, respectively (P = 0.493). Two patients (one man and one woman) died in the study period. In terms of underlying diseases, hypertension, type 2 diabetes mellitus (DM), hemodialysis, and emboli were found in 17, 13, 11, and 29 of patients, respectively. Moreover, one of the patients was addicted. 5 of the patients had a history of previous hospitalization and all of the patients were febrile.

The mean of ejection fraction (EF) was 45.00 ± 10.19 and 49.13 ± 7.33 among men and women, respectively (P = 0.103). The clinical features of patients have been shown in table 1.

Table 1. Clinical features of patients

Clinical finding	Sex		Total
	Man	Woman	
Emboli	16	13	29
Fever	27	23	50
Murmur	20	15	35
Hematuria	11	13	24
RF	10	11	21
Splinter hemorrhage	2	2	4
Conjunctival petechiae	2	2	4
Janeway lesion	2	1	3
Osler node	1	1	2

RF: Rheumatoid factor

Table 2. Procalcitonin (PCT) level, white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level at admission and at the end of treatment

Variable	At admission (mean ± SD)	At the end of treatment (mean ± SD)	P
Procalcitonin (ng/ml)	5.78 ± 3.13	14.12 ± 0.00	0.001
WBC count	14821.28 ± 5491.69	7282.20 ± 97.99	< 0.001
ESR (mm/hr)	74.24 ± 4.01	16.88 ± 7.08	< 0.001
CRP (mg/l)	71.24 ± 34.16	12.22 ± 5.28	0.003

WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

The mean of PCT at the time of admission was 6.44 ± 3.90 and 4.88 ± 2.24 among men and women, respectively (P = 0.316). At the end of treatment period, the mean of PCT level was 0.15 ± 0.13 and 0.14 ± 0.11 among men and women, respectively (P = 0.894). Other laboratory findings have been presented in tables 2 and 3.

There was not any significant linear correlation between PCT level at the time of admission and level of ESR (P = 0.148) and white blood cell (WBC) count (P = 0.343). However, the linear correlation between PCT level at the end of treatment and CRP level at this time (P = 0.012, r = 0.351) was significant.

There was not any significant linear correlation between PCT level at the end of treatment and ESR and WBC count at this time (P = 0.372 and P = 0.079, respectively).

The mean level of PCT at the time of admission was 6.90 ± 4.05 and 73.42 ± 4.20 among patients with positive and negative RF, respectively (P = 0.328). In addition, the mean level of PCT at the end of treatment was 0.135 ± 0.090 and 0.146 ± 0.120 among patients with positive and negative RF, respectively (P = 0.842).

Discussion

In this study, 50 patients with IE were evaluated in two referral centers of infectious diseases and cardiology in Tabriz University of Medical Sciences. The mean age of patients in this study was 50.24 years, which was less than the global mean age of the patients as 57.9 years.[11]

Man to woman ratio was 27/23. The dramatic incidence of disease was reported among men in most of the studies.[12,13] In a study conducted by Zencir et al.[2] on 59 patients with IE and 40 healthy controls, the mean age of the patients was 58.50 ± 14.70 years. In this study, the man to woman ratio in IE group was 25/34 and there was no significant difference with healthy group. IE was more common among men in the present study, which was different from the results of the study by Zencir et al.[2]

In the present study, positive blood culture (PBC) was detected among 36% of patients. Among them, staphylococcus aureus and streptococcus were more common. In another study by Mueller et al., all the patients with IE had PBC and staphylococcus aureus was the most common microorganism; which was found among 62% of patients.[14] In a study, blood culture was positive among 80% of patients and staphylococcus aureus was detected among 17% of them.[15] 62% of blood cultures were positive in another study.[16]

This significant difference in the rate of PBCs could be attributed to antibiotic therapy before definitive diagnosis that was usually took place among the feverish patients. Used culture methods, media, and low laboratory accuracy could be the other reasons. In another study, DM was found among 31% of patients with IE and there was no significant difference with healthy controls.[2] In the present study, 13 patients were diagnosed with DM. In a study on the risk factors of IE, presence of DM had significant correlation with development of IE among the patients with staphylococcus aureus bacteremia.[17]

Table 3. Procalcitonin (PCT) level among rheumatoid factor (RF) positive vs. RF negative patients

Variable	RF positive patients	RF negative patients	P
PCT at admission	6.90 ± 4.05	4.20 ± 73.42	0.328
PCT at the end of treatment	0.135 ± 0.090	0.146 ± 0.120	0.842

RF: Rheumatoid factor; PCT: Procalcitonin

High level of PCT was detected in blood in the course of bacterial infections with positive systemic inflammatory response syndrome (SIRS). In infection-induced inflammation, PCT synthesizes by macrophages, leucocytes and monocytes in various organs and neuroendocrine cells in lung and intestine. The most effective stimulator of PCT synthesis and release was the bacterial endotoxin and its synthesis was induced by tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), 1b, 2 and phytohemagglutinin.[9] PCT level was not increased in non-bacterial inflammations like viral infections and autoimmune diseases and bacterial infections which were limited to one organ except pneumonia. According to studies, PCT had prognostic value. High level of PCT is a sign of continuation of inflammation and poor prognosis and vice versa.[9]

In a case-report, the level of PCT did not increase in a patient with IE associated with streptococcus viridians. Therefore, it was stated that despite its proper specificity for diagnosis of IE, it did not have proper sensitivity. It is important to consider limitations of PCT for diagnosis of sepsis or IE, especially in emergency department.[9]

According to a review article about the role of acute phase reactants in infections, increase of PCT was less seen in inflammatory and non-infectious conditions, hence, it was a more sensitive, and specific marker in different infectious and non-infectious causes. In addition, its specificity was higher in comparison to ESR. Evidence has shown that use of PCT results in decrease of antibiotic use among patients admitted in the intensive care units (ICUs) and outpatients. However, more studies are required to evaluate its effect on mortality, morbidity and drug resistance.[8] In another study carried out on 59 patients with IE and 40 healthy patients, in-hospital mortality was compared with some parameters like vegetation size, CRP level, PCT level, neutrophil to lymphocyte ratio and platelet to lymphocyte. All of these parameters were higher significantly among the group with high ratio of in-hospital mortality.[2]

In another study conducted with the aim of diagnostic accuracy of PCT in the diagnosis of gram positive and gram negative blood infections and correlation of PCT level with infection site and type of pathogen, PCT had an important role in differentiating gram positive and gram negative bacterial infections. In addition, PCT is important in infections associated with different bacterial species and infections in different sites.[7]

According to a study by Schuetz et al., PCT had an important role in diagnosis of possible infection among patients with a history of heart problems referred with acute symptoms like dyspnea. PCT had a prognostic value, which was associated with clinical outcome and can be used as a guide for treatment.[6]

Studies showed that PCT had a significant correlation with bacteremia, which was an item in diagnosing of IE. In a cohort study on 1083 patients suspected of IE, PCT had strong correlation with PBC independent of type of pathogen or site of infection.[6]

In a systematic review, it was concluded that PCT was neither sensitive nor specific for IE; however, IE should be considered in the presence of fever, embolic phenomenon, new or changed murmur, risk factors for IE like valvar heart disease, intravenous (IV) drug abusers, and bacteremia with incomplete treatment, especially with staphylococcus aureus.[18]

According to Huang et al., serum level of CRP and PCT were valuable and reliable markers in early diagnosis and prognosis in sepsis patients.[19] According to Knudsen, PCT level was significantly higher among IE patients and PCT = 0.04 had a sensitivity and specificity of 95% and 12%, respectively.[15]

Similar to the previous studies, increased level of PCT was observed among IE patients, which decreased after treatment. Therefore, the PCT level at the end of treatment was significantly less than its level at the time of diagnosis.

Conclusion

In the present study, 50 patients with IE were

evaluated. Moreover, the serum level of PCT was measured at the time of diagnosis and at the end of treatment period. The mean of PCT level was 5.78 ± 3.13 and 14.12 ± 0.00 at the time of diagnosis and at the end of the treatment period, respectively. The mean of PCT level at the end of treatment period was significantly lower than its rate at the time of diagnosis. Average of WBC count, ESR and CRP level were lower significantly at the end of treatment period.

PCT can be a useful laboratory marker along with other laboratory (ESR, CRP, RF, etc.) and clinical features in primary diagnosis and evaluation of response to antibiotic treatment among patients with IE.

Acknowledgments

This work was supported fully by Infectious and Tropical Diseases Research Center (Grant NO 94-05), Tabriz University of Medical Sciences, Tabriz, Iran. This is a report of a database from thesis of Mr. Alireza Motallemi entitled "The Comparison of Serum Level of Procalcitonin in Patients with Bacterial Endocarditis at Diagnosis and at the end of Therapeutic Course Registered in Tabriz University of Medical Sciences".

Authors' Contribution

All of the authors contributed equally.

Funding

This research was supported by Infectious and Tropical Diseases Research Center (Grant NO 94-05), Tabriz University of Medical Sciences, Tabriz, Iran.

Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was approved by the Regional Medical Ethics Committee of Tabriz University of Medical Sciences under the number tbzmed.rec.1394.761.

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